# Investigating the effects of propofol-induced tonic inhibition on rhythmic neural activity in a hippocampal interneuron network

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## Motivation

- Propofol-induced sedation is achieved by positively modulating $GABA$ergic inhibitory activity [1]
- Synaptic and extrasynaptic $GABA_A$ receptors are ubiquitous in the brain [2]
- $GABA$ergic hippocampal interneurons have been shown capable of generating and maintaining $\gamma$-band $(20-80)\,Hz$ rhythmic neural activity [3]
- $\gamma$-band oscillations are thought to underlie long-term memory consolidation [4]
- We study the effect of the **propofol-induced extrasynaptic $GABA$ergic modulation** [5] on such self-emerging synchronous activity

## Neuron Model

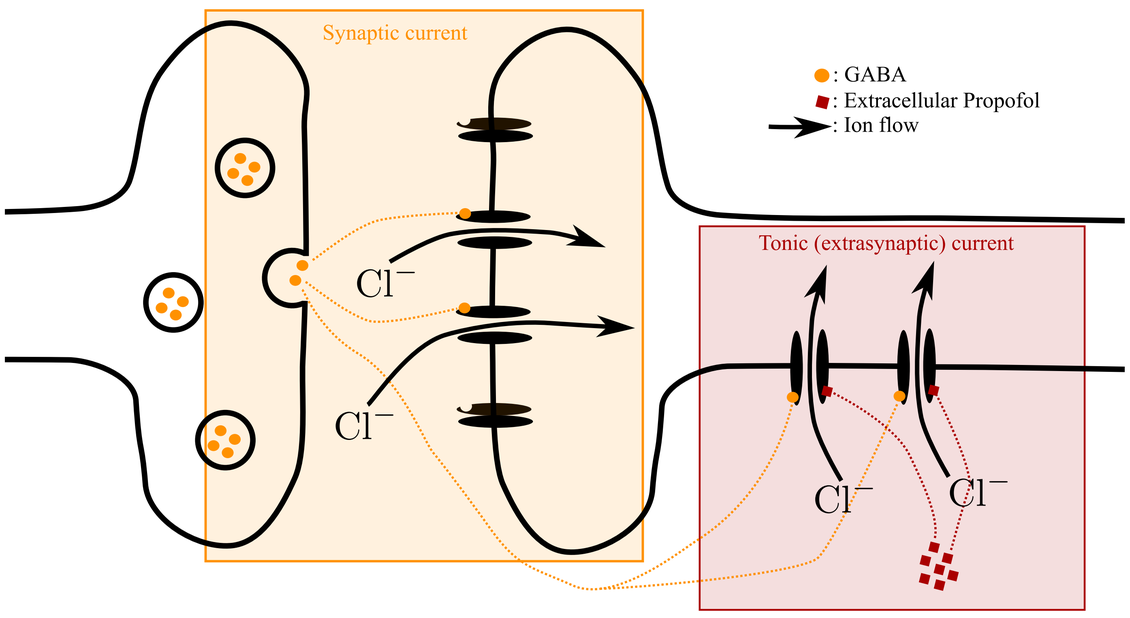
- Neuron Model:

$$C_m \cdot \frac{\mathrm{d}V}{\mathrm{d}t} = -I_L - I_K - I_{Na} - I_{Syn} - I_{SynTonic} + I_{Stim}$$

- Hodgkin-Huxley Currents and Stimulation:

$$I_{Leak} = f(V_m) \qquad I_K = f(V_m, n^4) \qquad I_{Na} = f(V_m, m^3, h) \qquad I_{Stim} = 0.4\,nA$$

## Synapses and Propofol




Schematic of $GABA$ (orange) binding on synaptic and extrasynaptic receptors causing $Cl^-$ ion influx in the postsynaptic neuron. Extrasynaptic $GABA$ receptors mediate tonic inhibition, and are potentiated by extracellular propofol (red). Propofol also binds on synaptic $GABA$ receptors (not modelled in the present work, thus not shown).

- Inhibitory Postsynaptic (Phasic) Current:

$$I_{Syn} = -g_i \cdot (V_m - E_i) \qquad \frac{\mathrm{d}g_i}{\mathrm{d}t} = -\frac{g_i}{\tau_i} \qquad g_i \leftarrow g_i + w_{ii}$$

- Inhibitory Extrasynaptic (Tonic) Current [5]:

$$I_{SynTonic} = -g_t \cdot (V_m - E_i) \qquad g_t \propto [\mathrm{C_{12}H_{18}O}]_o \quad \text{(propofol)}$$

- Network Topology:

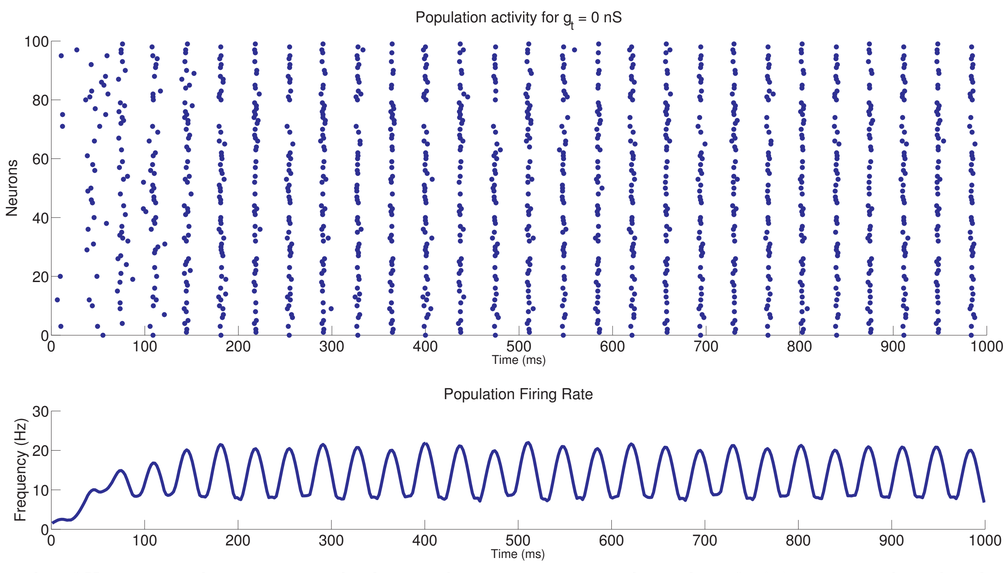
$$N = 100 \quad \text{(neurons)} \qquad \rho = 0.6 \quad \text{(connection probability)}$$

- Network Synchronisation Measure [3]:

$$\kappa_{i,j}(\tau) = \frac{\sum_{l=1}^{L} X_i(l) Y_j(l)}{\sqrt{\sum_{l=1}^{L} X_i(l) \sum_{l=1}^{L} Y_j(l)}} \qquad \kappa(\tau) = \frac{\sum_{i=1}^{N}\sum_{j=1}^{N} \kappa_{i,j}(\tau)}{N^2} \qquad 0 \le \kappa(\tau) \le 1$$

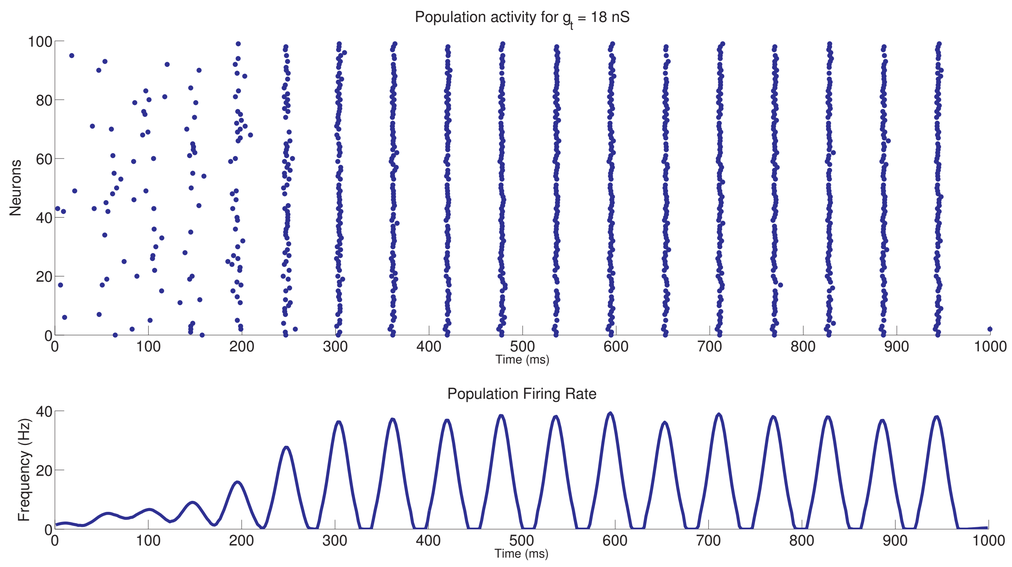
$$X_i(l), Y_j(l) \in \{0,1\} \qquad l = 0,1,2,...,L \qquad L = \frac{t_{sim}}{\tau} \qquad \tau = 10\,ms$$

## Results – $\gamma$-band Synchronisation

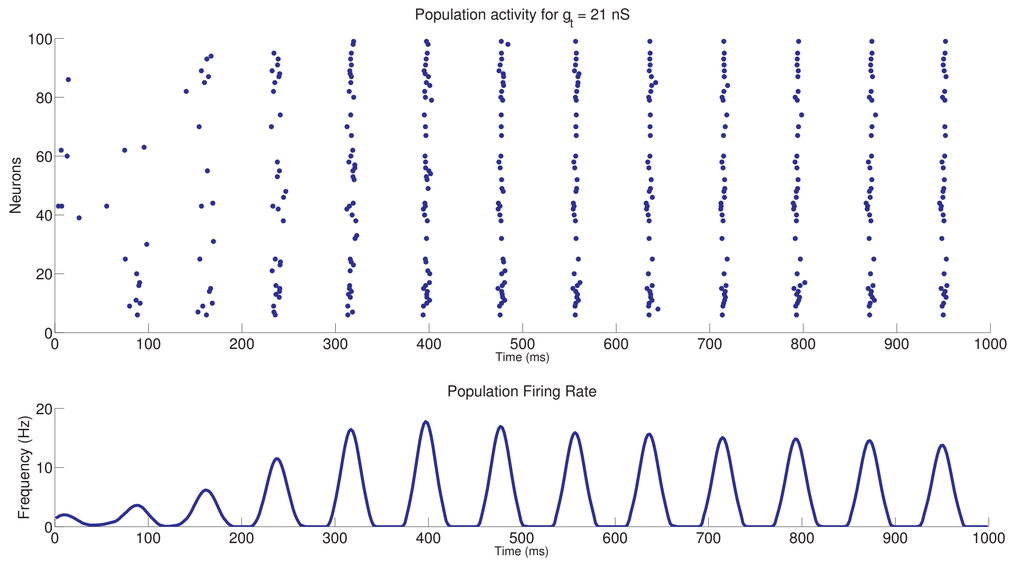



Networks of Hippocampal interneurons display synchronous activity with a value of $\kappa(\tau) = 0.4$, in the $\gamma$-band at an oscillatory frequency of $f_{osc} \simeq 25\,Hz$, when subject to a constant stimulation, in the absence of propofol.

## Results – Increasing Anaesthetic Dosage

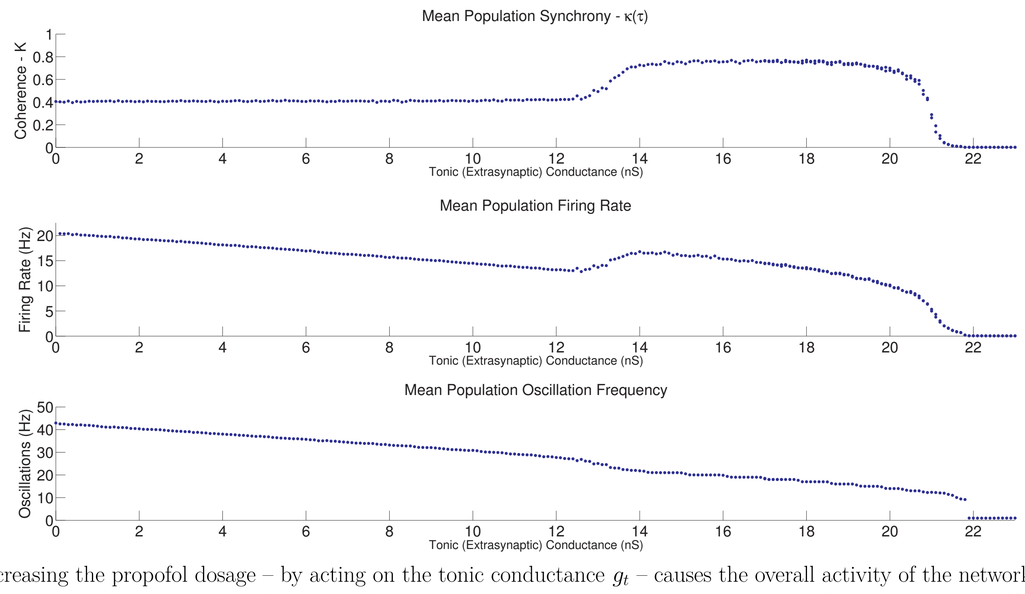



Increasing the dosage of propofol to $g_t = 18\,nS$ causes stronger synchrony amongst the neurons in the network $\kappa(\tau) = 0.8$, while slowing down the oscillatory activity to a frequency of $f_{osc} \simeq 15\,Hz$.




Increasing the dosage of propofol to $g_t \ge 21\,nS$ weakens the synchrony amongst the neurons in the network $\kappa(\tau) = 0.2$, and slows down the oscillatory activity to a frequency of $f_{osc} \simeq 10\,Hz$.

## Results – Propofol Synchrony and Oscillations




Increasing the propofol dosage – by acting on the tonic conductance $g_t$ – causes the overall activity of the network to decrease, until a critical value of $g_t = 14\,nS$ at which both the network synchronisation and firing rate increase. When the concentration value reaches a value of $g_t \ge 21\,nS$ the activity, synchronous or otherwise, fades out.

## Conclusion

- Anaesthetics target both synaptic and extrasynaptic $GABA_A$ receptors
- **Increasing the dosage of anaesthetic agents can strengthen synchronous activity** in networks of hippocampal neurons
- Paradoxical excitation behaviours might be mediated by the effects of anaesthetics on extrasynaptic $GABA_A$ receptors

## References

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